IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

IN RE:	**U.S.S.N. 09/518,165**	)
FILED:	**March 1, 2000**	)
TITLE:	**METHOD FOR DETECTING PRESENCE OF TARGET BACTERIA OR A TARGET COMPONENT CARBOHYDRATE ANTIGEN THEREOF**	)
		) **GROUP ART UNIT: 1645**
INVENTORS:	V.A. Koulchin, N.J. Moore, E.V. Molokova and M.K. Fent	) **EXAMINER: Ja-Na Hines**

BRIEF ON APPEAL

I. REAL PARTY IN INTEREST

The present application is assigned in its entirety to Binax, Inc., of 217 Read Street, Portland, Maine 04103, U.S.A., a corporation of the State of Delaware. Binax, Inc. is a small entity engaged in the development of medical diagnostic and related environmental tests which, upon concluding their development, it manufactures for sale.

II. RELATED APPEALS AND INTERFERENCES

There are no interferences known to the assignee, the named applicants, or their counsel that are in any way related to this appeal. No application owned by or assignable to Binax, Inc. is involved in an interference.

There are three other live patent applications that are related to this one, all of which are owned by the named applicants' assignee, Binax, Inc. Briefly stated, they are (a) U.S. Application Serial No. 09/139,720 filed August 25, 1998 which is still pending before the Examiner responsible for this application, (b) U.S. Application Serial No. 397,110 filed September 18,1999[1] which is a continuation-in-part of Serial No. 09/156,486 filed September 16, 1998, and is now abandoned in favor of its continuation-in-part application and (c) U.S. Serial No, 09/458,998, which is a continuation -in-part of U.S. Serial No. 09/139,720 and was filed December 10, 1999.

U.S. Application Serial No. 09/458,998 is presently the subject of an appeal from the same Examiner, notice of which was filed April 11, 2003.[2] A brief was duly filed in that appeal, with all requisite fees, on October 14, 2003, the first business day following October 11, 2003. By notice dated January 23, 2004, that brief was held by a Supervisory Patent Examiner to be defective for failure to comply with 37 C.F.R. 1.192 (c)(7) and the filing of a new brief was required. On March 23, 2004 a new Brief on Appeal was filed, accompanied by a Request under 37 C.F.R. 1.136 for a one month extension of time and the requisite small entity fee.

At this stage, counsel for applicants and their assignee is uncertain as to whether that brief is before the Board because on June 10, 2004 a further "Notice of Non-Compliance with 37 C.F.R. 1.192(c)", signed by the same Supervisory Patent Examiner, was received. This

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[1] Serial No. 397,110 was allowed on March 26, 2004 and the final fee was paid on June 25, 2004.

[2] The number of this appeal, if one has been assigned, has not been communicated to the named applicants, the assignee or their counsel.

notice alleged that the appeal itself is noncompliant with 37 C.F.R. 1.191(a) because "there has been no second or final rejection in this patent application". On June 16, 2004, counsel filed a "Response to Notification of Non-Compliance with 37 C.F.R.1.192(c) Mailed June 10, 2004 and Request for Reinstatement of Appeal" in which counsel demonstrated that all of the appealed claims 10-35, while concededly not *finally* rejected, *were twice rejected before appeal was taken.* It follows that the appeal complies fully with 37 C.F.R. 1.191(a) and since the June 10, 2004 notice alleges no other flaw, reinstatement of that appeal and transmission to this Honorable Board of the Appeal Brief filed March 23, 2004 are both required. However, no information as to the status of that appeal has to date been received.

The relationship of that appeal to this one resides both in the subject matter of each and in the similarity of the rejections that have been advanced in each of these appealed applications.

Each of these two appeals does involve claims covering immunoassays in which a crude bacterial carbohydrate antigen contained in a liquid sample is the target antigen. The detection agents in both instances are antibodies which have been affinity purified by passage over a chromatographic affinity column to which is bound, directly or through a coupling agent, a purified embodiment of the *same* carbohydrate antigen as the target antigen, containing no more (and preferably less) than 10% protein on a weight/weight basis.

In Application Serial No. 09/458,998 the assay disclosed and claimed is an enzyme immunoassay for detecting as little as 5-50 CFU (colony-forming units) of potentially infectious *Legionella* bacteria in environmental water by establishing the presence in the water of target O-carbohydrate antigen known to be characteristic of that *Legionella* species, or

serogroup of a species. In the present application, the broadest claim, Claim 53, is generic to the more specific assays disclosed and claimed in each of the co-pending, earlier filed applications 09/139,720, 09/397,110, 09/458,998 and the assays disclosed in this application *per se*. Apart from generic Claim 53, the assays claimed herein are immunochromatographic assays for detecting a selected carbohydrate target antigen characteristic of a given bacterial species, or serogroup of species, in a human bodily fluid obtained from a person suspected of being infected with a disease known to be caused by the bacteria of which the crude carbohydrate antigen is characteristic. Antibodies used to detect the target selected carbohydrate antigen in these immunochromatographic assays are treated in the same manner as those used in the assays of Application Serial No. 09/458,998.

The assay *details* covered in the claims of the two appeals are quite different. In Application Serial No. 09/58,998, the *Legionella* bacteria in the samples to be tested must be concentrated prior to undertaking the assay and certain of the appealed claims relate to or encompass preassay concentration method steps that are a part of the claimed invention. In addition, the bacteria in samples of environmental water are most often live and hence have hard, husklike shells that must be treated chemically, mechanically or both, in order to open their target carbohydrate antigens to the action of the antibodies.

In *this* appeal, putting aside the generic nature of Claim 53, the specifically claimed assays do not require preconcentration steps because the samples to be treated are human or other mammalian fluids such as urine, blood, etc. in which the bacteria, if present are relatively concentrated. The hard, husklike shells of live bacteria that may be present are not a problem because they have been at least opened (and often have been dissolved) by the activity

of various mammalian enzymes and/or the conditions indigenous to such organs as the kidney or liver.

Turning to the similarity of the rejections advanced, both in the appeal of Application Serial No. 09/458,998 and in this appeal, the Examiner has held that earlier filed, copending U.S. applications cannot be incorporated by reference under 35 U.S.C. §112. Issues of alleged double patenting, indefiniteness under 35 U.S.C. §112, (second paragraph) and enablement are also present in both appeals. The Examiner has placed reliance upon a fragmentary portion of "Critical Synergy: The Biotechnology Industry and Intellectual Property Protection," a document that is no longer available in its entirety even from the entity that issued it. in both of these appealed applications.

III. STATUS OF CLAIMS

The claims subject to this appeal are 23-25, 28-33, 35-42 and 53-59. Claims 3-22, 26, 27, 34, and 43-52 have been cancelled. Claims 1 and 2 have been retained in the application temporarily, pending the impending filing of a divisional or continuation application, but they stand withdrawn from consideration and will be cancelled before the Board reaches this appeal on its merits. A complete copy of appealed claims 23-25, 28-33, 35-42 and 53-59 is appended hereto as Appendix A.

IV. STATUS OF AMENDMENTS

All of the claims in Appendix A have been entered into the record.

In Appendix B hereto, Applicant proposes amendments to each of Claims 53-59 and seeks that those claims, as so amended, be entered for purposes of this appeal in lieu of their earlier, correspondingly numbered counterparts contained in Exhibit A.

V. SUMMARY OF INVENTION

The present invention involves a generic concept embracive of the contents of three earlier copending applications Serial No. 09/139,720, Serial No. 09/397,110, and Serial No. 09/458,998 and the content of the present application.

The essence of the generic concept is that particularly effective immunoassays for the detection, especially in a human bodily fluid or in an environmental sample, of bacteria known to be causative of human or other mammalian disease are attained by first selecting as the target of the assay, a carbohydrate antigen that is indigenous to and known to be specifically characteristic of the species, or serogroup, of a species of bacteria that causes a particular disease or other pathogenic condition.

As a first step, this carbohydrate antigen is then obtained from a culture of the bacteria in purified and essentially protein-free form–i.e. a form containing not more than 10%(wt./wt.) of protein. Many methods for so purifying carbohydrate antigens from bacterial cultures are known in the art and any of them may be selected for use. Methods for removing protein from carbohydrate antigens are also well known in the art.

The purified, essentially protein-free carbohydrate antigen may be employed in two alternative ways in this invention. In the second step of the process it is securely coupled to an affinity gel preferably by covalently binding it directly or through a coupling agent to the gel, placing the gel on an affinity column and purifying antibodies by passing them over the gel on the column. These antibodies may be raised against the starting bacteria by conventionally injecting a mammal, such as a rabbit, goat, pig, etc., with said bacteria at selected intervals over a period of weeks or months, as repeatedly described in the prior art, and then bleeding

the animal and recovering the antibodies by well known published methods. Alternatively and preferably, the antibodies maybe raised in an animal in the same conventional way by injecting the animal with crude target antigen or most preferably with the purified, essentially protein-free carbohydrate antigen as obtained in the first step of the process of this invention.

In any of these cases, the raw polyvalent antibodies obtained from the animal, or an antibody concentrate, such as an Ig G cut of the raw antibodies, are passed over the affinity gel to which the purified, essentially protein-free embodiment of the target carbohydrate antigen has been coupled. Upon elution of these antibodies from the gel, they exhibit high specificity for the crude target antigen in samples of human and environmental fluids and they are utilized, according to this invention, in immunoassays, particularly rapid immunochromatographic assays designed to detect the carbohydrate target antigen in human body fluids collected from individuals suspected of harboring a disease caused by the same bacteria species, or serogroup of a species, as the bacteria from which the target carbohydrate antigen was extracted. In the claimed assays for detecting the crude target carbohydrate antigens in human patient fluids (e.g. urine, blood, lymph, spinal tap fluid, middle ear fluid, etc.) an immunochromatographic strip having a sample introduction zone at one end and an endpoint zone near its other end is equipped with a movable deposit of labeled purified antibodies of this invention at a point located just forward of the sample introduction zone in the sample flow path. At the other end of the strip the endpoint zone consists of a strip of immovably deposited unlabelled antibodies spanning the width of the strip.

The sample, upon introduction to the strip flows forward and picks up the movably deposited labelled antibodies, which react with the target crude carbohydrate antigen if it is present in the sample as the two flow together along the strip, so as to form labelled antibody-antigen conjugates. As the labelled antibody-antigen conjugates reach the immovable stripe of unlabelled antibodies, they form an immovable labelled antibody-antigen-unlabelled antibody "sandwich" at the endpoint line which is detectable, due to massing of label on that line.

The preferred labelling agent is collidal gold but any other labelling agent capable of massing to form a discernible color, or eof xhibiting another detectable characteristic upon formation of "sandwiches" at the capture line, may be substitutued.

Summing up, the process steps of this invention, in its broadest form are:

(a) obtaining from the culture an embodiment of the target carbohydrate antigen that is essentially protein-free--a term defined in the specification (e.g. p.6, l.17; p.13, l.11) as meaning that the protein content is "not more than about 10% by weight"--(wt./wt. basis)[3];

(b) coupling this antigen embodiment to an affinity gel, directly or through a spacer molecule to produce a stable antigen-affinity gel conjugate, preferably one in which the antigen is covalently bound to the spacer molecule or the gel;

(c) passing crude polyclonal antibodies raised against the bacteria, or against the crude target antigen *per se* (Specification p.13, lines 1-7), in a mammal such as a rabbit, goat, etc., and obtained by conventionally bleeding the animal, over the affinity gel conjugate of step (b) and eluting from the gel antibodies having enhanced specificity for the crude target antigen,

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[3] Preferably, the protein content is less than this, but this defines an upper limit.

and

(d) conducting an assay upon a liquid sample suspected of containing the crude target antigen, such as urine, blood, spinal tap fluid, lymph, middle ear fluid etc., or contaminated environmental water (see specification p. 11, lines 7-22; see also copending Application Serial No. 09/458,998). For purposes of the assay, at least part of the antibodies are appropriately labelled with a tag that produces a detectable signal upon interaction of antibodies with crude antigen in the sample.

The invention as described is applicable to the detection of target carbohydrate antigens indigenous to Gram-stain negative bacteria, which antigens are, in general, known to be lipopolycarbohydrates and especially O-lipopolysaccharides as exemplified in incorporated-by reference copending earlier filed application Serial No. 09/139,720, and in its copending, continuation-in-part application Serial No. 09/458,998. The invention is also applicable to the detection of target carbohydrate antigens in Gram-stain positive bacteria which are, in general, teichoic and lipoteichoic acids and their derivatives, as is exemplified in earlier filed, copending Application Serial No. 09/397,110 which is fully incorporated herein by reference, and its now abandoned parent application, Serial No. 09/156,486. In addition, the examples of the present application show that the invention is applicable to detect those target carbohydrate antigens that occur in capsular form in both Gram-negative and Gram-positive bacteria.

The invention enables the development of immunochromatographic tests performable by almost anyone capable of reading and understanding the test directions within 15-20 minutes from sample introduction to reading of result, in any place, including locations remote from both hospitals and doctors. The tests are of high specificity and sensitivity and provide a

reliable basis upon which a physician may prescribe medication for a particular bacterially-caused disease or other condition. As Application Serial No. 09/458,998 demonstrates, the present invention encompasses other assays that may be performed on liquid samples in which the high-specificity antibodies obtained as described herein are substituted for prior art antibody preparations with improved specificity and sensivity.

VI. ISSUES PRESENTED FOR REVIEW

The following issues are presented for review:

1. Whether this application is entitled to incorporate by reference copending, earlier filed U.S. patent applications.

2. Whether this application is entitled to rely under 35 U.S.C. §120 upon the disclosures of each of U.S. application Serial No. 09/139,720 filed August 25, 1998, Serial No. 09/156,486 filed September 16, 1998, its continuation-in-part Serial No.09/397,110 filed September 16, 1999, and the continuation-in-part of Serial No. 09/139,720, Serial No. 458,998 filed December 1, 1999 for the disclosures contained in each.

3. Whether all claims are subject to rejection for failure to comply with 35 U.S.C. §112, first paragraph (item 6 of the December 11, 2003 action, pp. 6-13).

4. Whether Claim 24 is rejectable under 35 U.S.C. §112 first paragraph because it recites a "crude target carbohydrate antigen" which is "a lipoteichoic acid, a teichoic acid, or a derivative of either". (item 6 of the 12/11/03 action pp.13-14)

5. Whether all claims are subject to rejection under 35 U.S.C. §112, second paragraph (Item 8 of the 12/11/03 action p.14)

6. Whether the "metes and bounds" of Claim 24 and 36 are unclear and indefinite (Items 9 and 10 of the 12/11/ 03 rejection).

7. Whether all claims are subject to rejection for double patenting (12/11/03 rejection pp. 15-16).

8. Whether Claims 55-59 are subject to rejection under 35 U.S.C. §103(a) as unpatentable over Imrich *et al* U.S. Patent 5,415,994 in view of Barthe (J. Clin. Microbiol. 1988)

VII. GROUPING OF CLAIMS

A. Group I -- Claims 53, 23-25, and 28-33

Claim 53 of this application is its broadest claim. It generically covers the method for detecting in a fluid sample, a crude target carbohydrate antigen suspected of being present in said sample, using the series of steps, a-d inclusive, set forth at pp.8-9 hereof, *supra*. More precisely, Claim 53 recites the four method steps of

(a) obtaining a selected essentially protein-free target carbohydrate antigen (i.e. one containing not more than about 10% by weight of protein) from a culture of a preselected species, or serogroup of a species, of bacteria to which the crude form of said carbohydrate antigen is known to be indigenous,

(b) securely coupling said essentially-protein free embodiment of the target carbohydrate antigen to a chromatographic affinity gel,

(c) passing crude polyclonal antibodies which have been raised against the bacteria or the crude or purified target antigen in an animal over the chromatographic affinity gel of step (b) and eluting therefrom purified antibodies of high specificity for the crude target

carbohydrate antigen and

(d) conducting an assay upon a liquid sample suspected of containing the crude target carbohydrate antigen by contacting the sample with antibodies eluted in step (c) at least a part of which have been labelled with a tag known to manifest a detectable characteristic upon formation of an antibody-crude target antigen reaction product and noting the detectable characteristic as it appears.

More precisely, Claim 23 limits Claim 53 by requiring Gram-negative bacteria in its step (a) and specifying that the crude target carbohydrate antigen is a lipopolycarbohydrate; claim 24 limits Claim 53 by requiring Gram-positive bacteria in its step (a) and specifying that the crude target carbohydrate antigen is a lipoteichoic acid, a teichoic acid, or a derivative of either, and Claim 25 limits Claims 53 by specifying that the crude target carbohydrate antigen is a capsular polycarbohydrate antigen and that the bacteria of step (a) may be Gram- negative or Gram-positive. If the broad recitation of "bacteria" in claim 53 were held unpatentable , it would be necessary to consider the patentability of each of claims 23,24 and 25 separately.

Claim 28 limits Claims 53 by requiring the liquid sample in assay step (d) to be a natural fluid of mammalian origin; Claim 29 limits Claim 28 by requiring the liquid sample to be human urine and Claim 30 limits Claim 28 by requiring that the liquid sample be obtained from a human patient showing clinical signs of a disease known to be caused by the bacteria species, or serogroup of a species, present in step (a).

Claim 31 limits Claims 53 by requiring the assay of step (d) to be an immunoassay. Claim 32 limits Claim 31 by requiring the assay of step (d) to be an immunochromatographic assay. If claim 53 were held unpatentable, neither claim 31 nor claim 32 would necessarily be

unpatentable. Moreover, unpatentability of claim 31 would not necessarily render narrower claim 32 unpatentable.

Claim 33 limits Claim 32 to a process in which the bacteria of step (a) are *Haemophilus influenzae* type b and the crude target carbohydrate antigen is the capsular carbohydrate antigen of the same bacteria. Claim 33 is not necessarily unpatentable even if claim 32 were held to be so.

As to this group of claims, consisting of independent Claim 53 and its directly and indirectly dependent sub-claims 23-25 inclusive and 28-33 inclusive, the claims do not stand or fall together, as shown. Moreover, even if generic Claim 53 were held unpatentable, each of subclaims 23, 24 and 25 would need to be considered separately because each covers the process as applied to a separate subgenus of possible target bacterial carbohydrate antigens. Moreover, Claim 33, which directly depends on Claim 32, covers the process as applied a species of target bacterial antigen within the scope of Claim 25. Thus Claims 33 and 25 might fall together in that if Claim 25 as specifically described in this application were unpatentable, broader claim 25 might likewise be unpatenable on the same grounds; on the other hand, unpatentability of claims 25 would not necessarily foreclose patentability of claim 33.

B. Group II--Claims 54 and 35-42

Claim 54 is dependent on claim 53 and covers a species within the scope of claim 53 in which assay step (d) is limited to immunochromatographic ("ICT") assays and specifies the steps involved in performing them. If claim 53 were held impatentable based on some aspect of its broad assay step (d), it would still be necessary to consider the patentability of claim 54

separately from that of claim 53 and all of its directly and indirectly dependent claims.

Claims 35-38 and 41-are each directly dependent on claim 54, while claims 39, 40 and 42 are indirectly dependant on claim 54.

More specifically, claim 39 is dependent on claim 38, claim 41 depends on claim 39 and claim 42 depends on claim 39.

The patentability of each of claims 35, 36 and 37 needs to be considered separately from claim 54 because each deals with a subgroup of bacteria and bacterial carbohydrate antigens within the scope of claim 54 which is capable of being patentable separately from one another and separately from broader claim 54.

Each of claims 38-42, as now written, stands or falls with claim 54.

C. Group III--Claims 55-59

This group of claims covers an article of manufacture equipped to be sold. The broadest claim of the group is claim 55 and it is dependent upon claim 53 in that it recites that the prelabelled antibodies in the first zone of the ICT strip and the immovable antibodies in the second zone of that strip "have been obtained from step (c) of claim 53".

Were claim 53 to be held unpatentable, and claim 54 held to be patentable if written so as literally to include each of steps (a), (b), and (c), claim 55 would be rendered patentable by changing its dependency to claim 54.

Claims 56,57, 58 and 59 are each dependent on claim 55. Claims 56, 57 and 58 are each subgeneric to claim 55 in that each restricts the source of the antibodies to those having "enhanced sensitivity to a selected target carbohydrate antigen" of a different specified type of bacteria.

The patentability of claims 56, 57 and 58, assuming claim 53 is patentable, therefore does not necessarily stand or fall with that of claim 55 and each needs to be viewed separately if claims 55 is held unpatentable.

The patentability of claim 59, however, does stand or fall with that of claim 55.

D. General Statement Re Claim Groupings

All of the claims herein are primarily rejected on 35 U.S.C. §112 grounds, double patenting grounds and other formalisms. Rather than wasting the time of this Honorable Board by twice presenting the same discussion, e.g., as to why claims 53 and 54 and their respective directly and indirectly dependent claims are patentable, Appellants have chosen to demonstrate the support for the claims and the reasons why each is patentable in the "Argument" section of this Appeal Brief.

VIII. ARGUMENT

A. Issue #1--Incorporation By Reference

As pointed out in M.P.E.P. 608.01(p) (Rev.2 May, 2004) incorporation by reference of one or more copending commonly assigned, earlier filed U.S. patent disclosures into a later filed U.S. patent application is a proper way in which to proceed where the subject matter of the so-incorporated material is needed to support the claimed invention.

The concept here is of a generic method for detecting a preselected carbohydrate target antigen of a bacterial species, or serogroup of a species, in a liquid sample which comprises the broad steps of

a) obtaining from a culture of the bacterial species, or serogroup of a species, a purified, essentially protein-free (i.e. containing not more than 10% protein on a wt./wt. basis)

embodiment of the target carbohydrate antigen.

b) securely coupling the purified, essentially protein-free embodiment of the target antigen to an affinity gel,

c) passing antibodies raised in an animal against either the same bacterial species, or serogroup of a species, or the crude target antigen or its purified, essentially protein-free embodiment, over an affinity gel to which the purified, essentially protein-free, target antigen embodiment has been coupled and eluting therefrom antibodies of enhanced specificity to the crude target antigen.

d) employing said antibodies in a test for detection of the crude antigen in an unknown sample.

This application is generic insofar as it applies to detecting each of the following preselected carbohydrate target antigens:

(i) Gram-stain negative bacteria which have long been known in the art to constitute lipopolycarbohydrate antigens. Appellants' copending, commonly assigned patent application Ser No. 09/139,720 particularly describes an invention within the scope of this one for detecting a selected lipopolycarbohydrate antigen in a species, or serogroup of a species, of *Legionella* bacteria. In lieu of copying the disclosure of the earlier copending application into this one, the disclosure was incorporated herein by reference as of the filing date of this application.

(ii) Gram-stain positive bacteria, which have long been known in the art to be teichoic and lipoteichoic acids and derivatives of either. Appellant's copending, commonly assigned patent application Ser No. 09/397,110 particularly describes an invention within the scope of this one for detecting a selected target antigen of this group, the C-polysaccharide cell wall antigen common to all serogroups of *Streptococcus pneumoniae* bacteria

(iii) Preselected carbohydrate antigens occurring in capsulated form in both Gram-stain negative and Gram-stain positive bacteria.

Appellants' work relative to the capsulated carbohydrate antigen of *Haemophilus influenzae* type b is specifically described in this application.

The earlier applications incorporated herein by reference each contain at least one inventor in common with this application. They are in no sense comparable to the patents issued post-filing date to third parties, which were available as references under 35 U.S.C. §102 (e) against the applicant and were refused incorporation by reference *In in re Glass*, 492 F.2d 1228, 181 USPQ 3. (CCPA 1974) cited at p.4 of the Examiner's December 11, 2003 action from which this appeal was taken.

Appellants incorporated by reference the two copending, earlier filed applications referred to above *into this application* as filed. This incorporation by reference is strictly in accord with proper incorporation by reference as described in M.P.E.P. 608.01(p).

The similar incorporation by reference of commonly, assigned, copending application Serial NO. 09/458,998 herein *at the time of filing* is likewise appropriate. The present

application and incorporated-by-reference applications 09/139,720 and 09/397,110 all disclose employing immunochromatographic assays in, step d of the process of this invention, wherein the novel antibodies obtained in step (c) of the process of this invention are utilized as the detection agent for the corresponding crude carbohydrate antigen. Application Serial No. 09/458,998 describes a test for detecting from 5 to 50 colony-forming units of a *Legionella* bacteria, thus using antibodies obtained in step (c) of the process of this invention in a *different*, non-ICT assay--specifically an enzyme immunoassay--and thus exemplifying an assay that employs the highly specific antibodies of this invention to detect the crude target carbohydrate antigen in the bacteria found in environmental water samples. Step (d) of the invention as broadly recited in Claim 53 covers any assay in which the novel antibodies of the invention are the detection agent and incorporation of Application Serial No. 09/458,998 herein by reference provides specific support for the breadth of that claim.

B. Issue #2--Priority--35 U.S.C. §120

The discussion of "Priority" in the December 11, 2003 office action at pp.3-5 from which this appeal was taken misconceives the purpose for which the partial priorities of these prior applications are claimed.

Appellants have *at no* time urged that the generic concept disclosed and claimed in this application is entitled to a filing date earlier than its own March 1, 2000 filing date, and they do not now so urge.

What appellants *do* urge is the following:

a). Conception of the presently claimed process as applied to the detection of a preselected carbohydrate antigen indigenous to Gram-negative bacteria occurred upon

completion of work described therein and at least as early as the filing date of Application Serial No. 09/139,720 on August 25, 1998. Claims 23, 35 and 56 hereof are limited to this subgeneric concept.

b). Conception of the presently claimed process as applied to a preselected carbohydrate antigen of Gram-positive bacteria occurred upon completion of the work described in, and at least as early as the filing of Application Serial No. 09/156,486 (the now abandoned parent application of Serial No. 397,110) on September 16, 1996. Claims 24, 36 and 57 hereof are limited to this subgeneric concept.

c). Conception of the presently claimed process as applied to an encapsulated carbohydrate antigen of a Gram positive or Gram-negative bacterium occurred upon completion of the work described in the specific examples of this application and at least as early as its March 1, 2000 filing date.

d). Conception of the generic invention as recited in the broadest claim of this application, Claim 53, and of its dependent Claims 54 and 55 wherein step (d) of this invention is limited to performing ICT assays with the antibodies obtained according to this invention, occurred at least as early as the March 1, 2000 filing date of this application.

To sum up, the Examiner is correct that the broadest claims 53, 54 and 55 of this application could not be asserted or conceived of until at least one specific example was available of applying the process to a selected target carbohydrate antigen of each of a species, or serogroup of a species, of each of (i) Gram negative bacteria and (ii) Gram positive bacteria and also to (iii) a selected encapsulated antigen of a species, or serogroup of a species, of either Gram positive or Gram negative bacteria. That does not mean, however, that one could

not properly conceive of and assert one or more broad claims to the overall process once it was applied successfully to at least one member of each of the three groups.

C. Issue #3--Rejections Under 35 U.S.C. 112, First Paragraph

In making the "enablement" rejection, the Examiner appears to proceed upon the erroneous assumption that patentable invention may not be built upon information that exists in the prior art and is well known. This assumption appears to flow in part from the Examiner's interpretation of the documentary fragment, "Critical Synergy: The Biotechnology Industry and Intellectual Property Protection, Presentation of the Intellectual Property Committee of the Biotechnology Industry Organization at the October 17, 1994 Hearing of the U.S. Patent and Trademark Office, San Diego, CA, allegedley published by the Biotechnology Industry Organization Washington, D.C., p. 100-107[4].

The fragment is concerned with purification of proteins to infinitesimal degrees in the order of 2-3 decimal places and with recombinant DNA work, neither of which has any direct analogy to immunological assays, antigens and antibodies, or any other aspect of immunology-

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[4] The whole document is not available from the Examiner, nor does she know of any library from which it might be obtained, despite the comments made at pages 9-10 of the Dec. 11, 2003 action. She acknowledged this in a telephone conversation held in connection with preparation of Appellants' response to an earlier action in which this document was first cited.

Meanwhile Appellant's counsel, with the assistance of a trained librarian has endeavored to obtain the whole document from its alleged publisher, the Biotechnology Industry Organization, which said that it is not longer available, and from a number of other libraries including the U.S.P.T.O. Biotech Library, the USPTO Scientific and Technical Library and Center, the patent Depository Library in San Diego, CA., the U.S. Dept of Commerce Library, the USPTO Office of the Solicitor, the U.S. Library of Congress, the U.S. Senate Library, the Canada Institute of Science and Technology, Lexis, Westlaw, The British Library, the Linda Hall Library of Science, Engineering and Technology and the Georgetown University Federal Depositary and Law Libraries, all without success.

-a relatively mature science.

The specification of this application discloses, and the Affidavit of record of William J. Palin, Ph.D., vice President of Research at Binax, Inc. since 2001 (a date after the present application was filed.) confirms, that a vast body of literature exists with regard to how to purify antigens from bacterial cultures, how to render them essentially protein free and how to bind them to affinity matrices. See this Affidavit, Appendix C hereto, which was filed on August 25, 2003 and which rebuts the Examiner's contentions and premises that one of ordinary skill in immunology could not easily practice the claimed invention, especially in its ¶¶7-16 inclusive.

The Examiner neither acknowledged nor commented upon this affidavit in the ensuing action of December 11, 2003 and Appellants note that a Request for Remand to the Examiner, for the specific purpose of eliciting the Examiner's comments on the Affidavit, made concurrently with the filing of the Notice of Appeal herein, was neither acted upon nor responded to, thereby rendering the preparation of this Appeal Brief extremely difficult in the circumstance that the Examiner will comment on the Affidavit, if at all, in response to this Brief, when Appellants may be inhibited as to the points raised by the Examiner upon which their reply brief may comment or offer rebuttal.

The Examiner adheres in connection with 35 U.S.C. §112, first paragraph, to a rejection that no teaching has been made of a method for detection in which the steps of (a) obtaining a purified, essentially protein free, carbohydrate antigen from a bacterial culture, (b) conjugating the purified antigen stably to an affinity gel, (c) passing crude antibodies over the affinity gel and eluting therefrom purified antibodies of improved specificity and sensitivity

and (d) then utilizing those antibodies as detection agents in an assay, can be done successively in one place at one time as a continuous hybrid method.

This rejection is unprecedented insofar as Appellants' counsel has been able to determine. It has never been applied in any case that counsel has been able to locate, anywhere, even though a concerted effort to find such a case has been made. It has no precedent in the M.P.E.P. or the rules. The Examiner has likewise furnished no justification for the premise that the methodology of an application must be conducted "as one method" continuously. This rejection is untenable and should be reversed.

In the action appealed from at p.6 the assertion is made that "The specification teaches that *some* Gram-negative bacteria possess lipopolysaccharide or lipo-polycarbohydrate antigens and Gram-positive bacteria and Gram-positive bacteria generally possess lipoteichoic acid or teichoic acid (page 2)."[5]

The implication here is that this "teaching" was discovered by applicants. The *fact* is that the literature, including technical dictionaries in existence long before Appellants' filing date, has consistently taught that the carbohydrate antigens of Gram-negative bacteria are, in general, lippolysaccharides and the carbohydrate antigens of Gram-positive bacteria are, in general, teichoic and lipoteichoic acids and their derivatives. Ignored is the fact that Appellants teach, and illustrate, in the specific example of the present application that the methodology claimed also pertains to *encapsulated* carbohydrate antigens of *both* Gram-

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[5] The word "some" in this quotation constitutes the Examiner's self-serving imposition of a limitation upon what the art teaches as "in general" i.e., the rule of "as far as is known."

positive and Gram-negative bacteria.

Though it is not specifically clearly stated, it appears that a part of the 35 U.S.C. §112, first paragraph, rejection is a contention that the method of purification of each and every bacterial carbohydrate antigen must be identical to be patentable--a premise that appears intrinsic to the assertion (Dec 11, 2003 action, p.7) that "First the art [of] purification is highly unpredictable". This assertion,however, is inaccurate, as is clear from the specification at page 14 that "Many methods for effecting these [antigen] purification and separation steps are known in the literature and may be substituted for those herein described without departing from the scope of this invention, so long as the purified antigen is essentially protein free as herein decribed."[6]

The Examiner at p.8 of the Dec. 11, 2003 action ignores the very essence of immunology. Literature in existence before the filing date hereof describes the various carbohydrate antigens indigenous to most or all disease-causing bacteria. By preselecting a carbohydrate antigen, the presence of which is specific to, and hence characteristic, of a given species, or serotype of a species, of bacteria, one can readily select from the literature a purification method and a technique for reducing its protein content to not more than 10% or less, on a wt./wt. basis. From suppliers' literature and other writings contained in journals, etc., one can select an appropriate affinity gel to which the purified, essentially protein free antigen can be stably bound. Immunologists know very well that polyvalent antibodies can be raised in animals, such as rabbits, goats, etc by multiply injecting the animal over a selected

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[6] I.e., "essentially protein free" means containing not more than 10% protein on a wt./wt. basis.

time period, with the bacteria from which the carbohydrate antigen was obtained or with the crude antigen, or even another antigen form such its purified, essentially protein free embodiment as herein required. The broad process of affinity purification is not *per se* new (albeit the form of such purification disclosed herein, with the purified, essentially protein free antigen embodiment is new). Immunologists are readily able to pass antibodies over a prepared affinity gel, to which purified essentially protein-free antigen has been coupled and then elute the most specific fraction, as determined applying well published, well established techniques, and utilize that fraction in assays as herein described.

Appellants have never contended that the purified antibodies obtained according to this invention are capable of reacting with *any* bacterial carbohydrate antigen in an unknown sample, and the Examiner's statement at p.8 of the Dec. 11, 2003 addition that "Applicants have failed to make antibodies that can target *any* bacterial antigen in the sample" makes no sense in terms of the science of immunology. The antibodies obtained according to this invention target *only* the specific crude antigen in a sample that corresponds to the purified, essentially protein free antigen over which the antibodies were affinity-purified. Indeed, it is this which is the ultimate achievement of this invention--Appellants have developed a method by which polyvalent antibodies can be treated effectively so that they will zero in on the target crude carbohydrate antigen present in the sample. This target carbohydrate antigen is preselected based on literature showing it to be inextricably linked to a particular species, or serogroup of a species, of bacteria known to be causative of a given disease state and is therefore intended to be a means of identifying *that bacteria*. The polyvalent antibodies are effectively fine-tuned to detect only that target carbohydrate antigen, if present in the sample,

and to detect nothing, if the target bacteria are absent from the sample. A rapid test allowing the crude antigen to be detected in human body fluids (e.g., urine , blood, etc.) within 15-20 minutes is accordingly invaluable in ruling in or ruling out the presence of a specific disease caused by the specific bacteria which, it is already known, can be identified by the presence of the crude carbohydrate antigen which the antibodies have been fine-tuned and conditioned to recognize selectively, as a direct result of being earlier passed over the affinity gel to which a purified, essentially protein free embodiment of the same crude antigen was stably coupled.

This is the essence of why the present invention is highly important to the improvement of medical diagnoses of diseases known to be caused by specific bacteria. The Appellants' already commercialized assays for *Streptococcus pneumoniae* and *Legionella pneumophila* serogroup 1 have eliminated the need for time-consuming and often errorprone bacterial cultures. They have, respectively, changed the face of diagnosis in regard to classical pneumonia (and other *S. pneumoniae*-caused disease states that have different clinical manifestations such as bacteremia, infectious meningitis and otitis media) and Legionnaire's disease. Rapid diagnosis in turn, has enabled more timely and efficient medication of patients.

This generic invention offers similar advantages in diagnosing diseases caused by other bacteria that are characterizable by their possession of carbohydrate antigens by which each may be uniquely identified.

The Examiner's speculation at pp.8-9 of the Dec. 11, 2003 action that "one would have to know at the outset what type of bacteria a person was infected with because that person would then have to use polyclonal antibodies raised to that target carbohydrate antigen in the [affinity(?)] gel" makes no sense at all.

Bacterially caused diseases have already been correlated to particular bacteria. The carbohydrate antigens indigenous to disease-causing bacteria are reported in the literature and it is possible to select one for a given species, or serogroup of a species, of bacteria that is unique to it. Tests can therefore be readily devised according to this invention that allow medical personnel to rule in or rule out diseases caused by specific bacteria on the basis of whether a carbohydrate antigen unique to each specific species, or serogroup of a species, of bacteria appears in a patient sample.

The Examiner misstates on p.9 of the Dec. 11, 2003 action that "Applicants claim that the only patentable aspect of the claims is the antibodies bodies [sic]". Appellants, to the contrary, contend that the methodology as covered by the claims is patentable and that the key to its patenability lies in the development of a method that produces antibodies of high specificity for a preselected crude bacterial antigen, which do not exhibit cross-reactivity or high background and yield an assay of high specificity (usually 95-100%) and high sensitivity as well, which allows confident positive diagnosis when the target carbohydrate antigen is present in the sample and allows an equally confident negative answer when the assay shows the target carbohydrate antigen to be absent from the sample.

At p.10 of the Dec. 11, 2003 office action, the Examiner repeats previously raised assertions which show that the art and science of immunology is not being and has not been understood. In the first place, an essentially protein-free carbohydrate antigen--i.e. one containing not more than 10% protein--is an ascertainable product and not a "functional limitation" as alleged. In the second place, the specificity of a given antibody preparation for a particular antigen is frequently determined in immunology and can readily be determined here.

In the third place, with the wealth of literature that exists relative to carbohydrate antigen purification and protein reduction in antigen preparations, as set forth in the Palin affidavit, the process is not "empirical" and can readily be achieved by one of ordinary skill in immunology. Furthermore, the present specification clearly teaches in its examples the method that Appellants used to achieve an essentially protein-free embodiment of the capsular carbohydrate antigen of *Haemophilus influenzae* type b and through incorporation by reference of the examples of each of Applications 09/139,720 and 09/397,110 it clearly teaches, in the respective examples of each, how to achieve an essentially protein-free embodiment of an O-polycarbohydrate, specifically the O-polysaccharide antigen of *Legionella pneumophila* serogroup 1 and an essentially protein-free embodiment of the C-polycarbohydrate-specifically the C-polysaccharide cell wall antigen of *Streptococcus pneumoniae*. The O-polysaccharide antigen of *Legionella pneumophila* serogroup 1 is unique to that serogroup of the *L. pneumophila* species; the C-polysaccharide cell wall antigen of *S. pneumoniae* is unique to and characteristic of the entire *S. pneumoniae* species.

And while there may be many columns, gradients, affinity gels, buffers, etc that could be used in achieving an essentially protein-free embodiment of a selected carbohydrate antigen, one of ordinary skill with the prior literature pertinent to the selected carbohydrate antigen before him *can* readily determine, without undue experimentation, an effective way of reaching the desired goal, as indeed the Palin affidavit clearly suggests.

The pretended "unpredictability" and "complexity" (Dec. 11, 2003 action p.11) in this art is a red herring, as the Palin affidavit also shows.

No claim of this application "requires" addition of Tween 20, sodium azide and sodium dodecyl sulfate in sodium citrate phosphate buffer "to produce the crude carbohydrate antigen" because that is not the purpose of adding two drops of that buffer mixture to the sample. The Palin affidavit in ¶16(d), (e) and (d) at pp. 10-14 shows that the Examiner's assumption is false; its ¶16 (d) (pp.13-14) further states the actual purpose of each of the ingredients in that buffer, which is far removed from what the Examiner speculates.

At pages 11-12, the Dec. 11, 2003 action engages in further speculation that is very difficult to understand. The prior literature shows specific purification methods for obtaining selected target carbohydrate antigens of both Gram-positive and Gram-negative bacteria and the incorporated by reference applications Serial No. 09/139,720 and 09/397,110 exemplify the specific methods Appellants used to obtain identified selected carbohydrate target antigens in essentially protein-free purified form. Appellants have consistently *denied* and they again *deny* that a method for "extraction" of antigen in a sample is addressed anywhere except in Application Serial No. 09/458,998. In that application there is disclosed a so-called "extraction agent" for opening up the tough, husklike walls of *Legionella pneumophila* serogroup 1 whole bacteria, many of them living, that exist in contaminated environmental water dangerous to humans who contact it. Appellants have so far found, neither in their work specifically disclosed in this application and in the incorporated by reference applications 09/139/720 and 09/397,110,nor in their ensuing work since the filing of this application relating to developing assays for selected carbohydrate target antigens unique to other and further bacteria, any need to "extract" carbohydrate antigens present in human fluid samples in order to be able to detect them.

The discussion at pages 12-13 of the December 11, 2003 action beginning with "The use of any carbohydrate antigen would not predictably result in a detectable crude antigen" is not understood. In the first place, this application does not propose "the use of any carbohydrate antigen" but instead suggests that a selected carbohydrate antigen known to uniquely define a particular disease causing bacteria species, or serogroup of a species be the starting point of the claimed methodology Claims 53-58 inclusive have been amended in Appendix B to make this point very clear.

In the second place, the discussion on page 13 of the action appears to attempt to relate the cited paragraph on page 12 to the fact that the specification, based on the prior art, states that Gram-positive bacteria contain carbohydrate antigens that may be teichoic or lipoteichoic acids, or derivatives of either. Appellants do not propose in this application to *make* esters of either acid, or to *make* any other derivative of either acid.

What they *do* propose is that a carbohydrate antigen which is unique to a particular Gram-positive bacteria, may be, as the prior art teaches, a teichoic or lipoteichoic acid or a derivative of either. Appellant's application teaches that if such a carbohydrate antigen is selected for treatment according to the methodology of Claims 53-54, to can in fact be treated exactly as the method steps prescribe, by isolating a purified essentially protein-free antigen embodiment, coupling that embodiment to an affinity gel, purifying crude polyclonal antibodies to the antigen or the host bacteria by passing them over the affinity gel to which the purified protein free antigen embodiment has been coupled and then employing the antibodies to detect the selected crude carbohydrate antigen in a sample. No special guidance is needed to do this and the Examiner has shown no concrete reason of any nature by which one might

reasonably presuppose that the method would fail to work on an antigen that was an ester derivative of teichoic or lipoteichoic acid.

Furthermore, appellants would *not,* in any case, following the disclosure of this application, "use esters of lipoteichoic or teichoic acid to detect the crude antigen". (Action p.10) Even if the preselected crude carbohydrate antigen *should be* an ester, the methodology of the application would employ purified *antibodies* to detect it and basic principles of immunology teach clearly that this would work.

Withdrawal of the rejection is appropriate and is requested.

D. The Rejection of Claim 24 in Paragraph 7 of the December 11, 2003 Office Action as "New Matter" is Ill -conceived

Claim 24 has been singled out for this rejection because it specifically refers to carbohydrate antigens of Gram-positive bacteria as teichoic and lipoteichoic acids and derivatives of each, as the prior art discloses them to be. Antigens behave as antigens immunologically, whatever their chemical functional groups may be. When antigens have such functional groups, as ester groups, antibodies can still be raised to them and immunological reactions of binding between antigen and antibodies take place just as they do if the antigens have acid or-OH or other simple functional groups. The suggestion that ordinary immunological relationships would be wholly suspended if the selected target carbohydrate antigen unique to a particular bacteria species were, e.g., an ester of teichoic acid, has no basis in any fact that has been advanced by the Examiner and does not make sense from the viewpoint of immunology. The rejection is pure speculation without any foundation whatever.

The portion of the discussion in ¶7 of the rejection that appears on page 14 of the

action that "there appears to be no support in the specification for using the claimed purification steps to specifically purify Haemophilus antigen" is not comprehensible. The selected purified, essentially protein-free carbohydrate target antigen recovered as described in the Examples, from a culture of *Haemophilus influenzae* type b is the known capsular polycarbohydrate antigen of this bacterium. There are *no* "*claimed* purification steps", however. The "claimed" steps are recovering the purified, essentially protein-free antigen embodiment from a bacterial culture; coupling that antigen embodiment to an affinity gel and passing crude polyclonal antibodies over that gel to affinity purify them. Use of these antibodies as detection agents in an assay for the crude target antigen in samples is also disclosed in the examples in detail.

E. Rejection of all Claims
Under 35 U.S.C. 112, Second Paragraph

As expressed in this action, the essence of this rejection is the assertion that "it is unclear how one can determine which antibodies are now enhanced" (Dec. 11, 2003 Action, p.14, ¶8).

As every immunologist of ordinary skill in the art will readily recognize, the enhanced specificity of the purified antigens is determined by using them to detect the crude target carbohydrate antigen in samples of human urine known to contain the target antigen, as is disclosed in the specification's examples, and then making a simple routine calculation well known in the art of immunology. It does *not* involve separating the antibody mixture into individual antibody components, as suggested by the Examiner's comment.

F. The Rejection Relating to the "Metes and Bounds" of Claims 24 and 36

This rejection is again an effort to deprive Appellants of the full definition that the prior art provides for the carbohydrate antigens of Gram-positive bacteria--i.e. that they are, in general, lipoteichoic and teichoic acids and derivatives of either. Appellants did not create the prior art definition, nor have they had any occasion to *make* derivatives of teichoic or lipoteichoic acids. The literature contains many articles purporting to disclose the chemical structure of various known carbohydrate antigens, of which there are many. The literature, including chemical dictionaries, would not define the carbohydrate antigens of Gram-positive bacteria, "in general" as inclusive of derivatives of teichoic and lipoteichoic acids unless that were the fact.

The claims to which this rejection applies do not become either unclear on indefinite by virtue of the fact that Appellants have made no massive investigation to identify every carbohydrate antigen that is a "derivative" of a teichoic acid or lipoteichoic acid. The criticisms of claims 24 and 36, in each instance, are simply a repudiation of what the prior art has been comfortable in ascribing to the carbohydrate antigens of Gram-positive bacteria. As already noted, there is no basis on which it can be shown that 'derivatives" of either teichoic acids or lipoteichoic acids would behave immunologically, as antigens, in any different way from their parent acids. The "metes and bounds" of the two claims are seemingly cabined by the "derivatives' disclosed in the prior art and--whatever their structures may be--they are antigens which Appellants would expect to obey normal principles of immunology and hence to be usable in the claimed methodology of this invention.

G. The Double Patenting Rejection

Appellants have made of record heretofore that the rejection of various claims herein for double patenting over the claims of copending Applications Serial Nos. 09/458,998, 09/397,110-(and presumably also 09/139,720 though this is not stated in the Dec. 11, 2003 action at pp. 15-16) will be removed by the filing of a terminal disclaimer that makes the term of all patents of the group co-terminous with that of the first to issue.

Presumably the first to issue will be Serial No. 09/397,110 which is allowed and has had its final fee paid. Therefore, it is likely that this terminal disclaimer will have been made of record herein before this Board reaches the appeal in this application.

H. The Rejection of Claims 55-59 Over Imrich *et al* US Patent 55,415,994 in view of Barthe *et al* (J. Clin. Micro 1988) - 35 U.S.C. §103

This rejection is ill taken. 35 U.S.C. §103 requires *in terms* that "the differences" between the claimed subject matter and the prior art be "such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill" in immunology.

Neither Imrich nor Barthe teaches or suggests any way by which polyclonal antibodies to any carbohydrate antigen *could be* treated to confer enhanced specificity upon them. The claims require that all of the antibodies used in claims 55-59 in both zones of the ICT strip be "obtained" in step (c) of Claim 53". Antibodies so obtained have been passed over a purified, essentially protein-free carbohydrate antigen coupled to an affinity gel and eluted therefrom prior to being applied to the ICT strip. Such affinity purification is shown, e.g., in

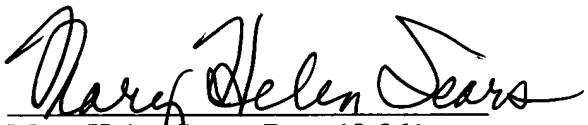
incorporated-by-reference Application 09/139,720 to increase the specificity, for the C-polysaccharide antigen of *Legionella pneumophila* serogroup 1, of antibodies raised against that specific bacterium or its polysaccharide antigen. No antibody disclosed by Barthe *et al* has been affinity purified. Neither Barthe *et al* nor Imrich suggests that there is any advantage to be gained from affinity purifying antibodies, much less from the specific affinity purification steps described and claimed in Application 09/139,720. In short, the rejection is based on a combination of two references, neither of which describes or suggests Appellants' methodology. Appellants' methodology, however, is critical to applicant's results. The Examiner's speculations about "functionally equivalent" results do not supply the methodology or result of Appellant's "invention as a whole" and, therefore, Claims 55-59 are not properly rejected under 35 U.S.C. §103.

CONCLUSION

The various rejections advanced by the Examiner in the Dec. 11, 2003 action from which appeal was taken are lacking in merit and rest to a significant extent upon distortion and misunderstanding of appellant's disclosure and the disclosures of the copending, commonly assigned applications incorporated herein by reference.

Reversal of these rejections is requested.

Respectfully submitted,



Mary Helen Sears, Reg. 19,961
Attorney for Appellants
The M.H. Sears Law Firm, Chartered
910 Seventeenth Street, N.W., Suite #800
Washington, D.C. 20006
Telephone: (202) 463-3892
Telecopy: (202) 463-4852

APPENDIX A--APPEALED CLAIMS

23 The method of claim 53 in which the species, or serogroup of a species, of bacteria in step (a) are gram-negative bacteria and the crude target carbohydrate antigen component thereof sought to be detected in step (d) is a lipopolycarbohydrate;

24 The method of claim 53 in which the species, or serogroup of a species, of bacteria in step (a) are gram positive bacteria and the crude target carbohydrate antigen component thereof sought to be detected in step (d) is a lipoteichoic acid, a teichoic acid, or a derivative of either;

25 The method of claim 53 in which the species, or serogroup of a species, of bacteria in step (a) are either gram-negative or gram-positive bacteria and the target carbohydrate antigen component thereof sought to be detected in step (d) is a capsular polycarbohydrate antigen;

28 The method of claim 53 wherein the liquid sample of step (d) is a natural fluid of mammalian origin;

29 The method of claim 28 wherein the liquid sample of step (d) is human urine;

30 The method of claim 28 wherein the liquid sample of step (d) is obtained from a human patient exhibiting clinical signs of a disease known to be caused by the selected species, or selected serogroup of a species, of bacteria referred to in step (a);

31 The method of claim 53 in which step (d) is an immunoassay process;

32 The method of claim 31 in which step (d) is an immunochromatographic ("ICT") process;

33 The method of claim 32 in which the bacteria referred to in step (a) are *Haemophilus influenzae* type b bacteria and the crude target carbohydrate antigen sought to be detected in step (d) is the capsular carbohydrate antigen of those bacteria;

35 The method of claim 54 in which the bacteria are gram-negative bacteria and the characteristic crude target carbohydrate antigen sought to be detected is a lipopolycarbohydrate antigen;

36 The method of claim 54 in which the bacteria are gram-positive bacteria and the characteristic crude target carbohydrate antigen sought to be detected is a lipoteichoic acid, a teichoic acid, or a derivative of either;

37 The method of claim 54 in which the bacteria are gram-positive or gram-negative bacteria and the characteristic crude target carbohydrate antigen sought to be detected is a capsular carbohydrate antigen;

38 The method claim 54 in which the liquid sample is a natural fluid of mammalian origin;

39 The method of claim 38 in which the liquid sample is human urine;

40 The method of claim 39 in which the liquid sample is obtained from a human patient exhibiting symptoms of a disease known to be caused by the species, or serogroup of a species, of bacteria of which the crude target carbohydrate antigen is known to be characteristic;

41 The method of claim 54 in which the labelling agent is finely divided gold;

42 The method of claim 39 in which the crude target carbohydrate antigen sought to be detected is the capsular carbohydrate antigen of *Haemophilus influenzae* type b;

53 A method for detecting the presence in a fluid sample of a target carbohydrate antigen

characteristic of a selected species, or a selected serogroup of a species, of bacteria which comprises the following steps:

(a) obtaining from a culture of the selected species, or selected serogroup of a species, of bacteria an embodiment of said target carbohydrate antigen that is essentially protein-free,

(b) coupling said essentially protein-free embodiment of said target carbohydrate antigen from step (a) to a chromatographic affinity gel,

(c) passing polyclonal antibodies raised in a mammal against said bacteria or said target carbohydrate antigen in crude form, over the chromatographic affinity gel obtained in step (b) and eluting there from antibodies with enhanced specifity to the said target carbohydrate antigen, and

(d) conducting an assay upon a liquid sample suspected of containing the crude target carbohydrate antigen, which assay comprises the steps of

(i) contacting the liquid sample with a detection agent comprising antibodies with enhanced specificity to said target carbohydrate antigen obtained in step (c) hereof, at least a portion of which have been labelled with a labelling agent known to manifest a detectable characteristic upon the formation of a reaction product between said antibodies and said crude target carbohydrate antigen and

(ii) detecting the presence in the sample, when present, of

said crude target carbohydrate antigen by observing the manifestation of said detectable characteristic therein

54 The method of Claim 53 in which step (d) comprises an ICT assay conducted in an ICT device comprising a strip of bibulous material disposed laterally within a housing, which housing is equipped with a view window and wherein said strip of bibulous material comprises at least (1) a first zone in which is deposited, at a location near the sample receiving end of the strip a moveable deposit of antibodies obtained in step (c) of Claim 53 having enhanced specificity to said target carbohydrate antigen, which antibodies have been labelled prior to being so deposited with a labelling agent selected from among those labelling agents which display a visible color change upon the formation of a labelled antibody-antigen-immovable antibody reaction product, and (2) a second zone so positioned that it is near the opposite end of said strip relative to the first zone and is observable through the view window in the housing of said ICT device, in which another portion of antibodies obtained in step (c) of Claim 53 have been immovably bound to said strip, and the ICT assay is carried out by;

(a) contacting said liquid sample with said strip at its sample receiving end,

(b) allowing said sample to flow laterally into said first zone and pick up said moveable deposit of labelled antibodies that has been placed there,

(c) allowing said sample and said conjugate to flow together laterally to said second zone while in intimate contact with one another, thereby enabling target carbohydrate antigen, if present in the sample, to react at least partially with said conjugate to form further labelled antibody-antigen

conjugates,

(d) allowing the laterally flowing stream from step (C) to flow into said second zone and contact said antibodies immovably bound to said strip and

(e) within approximately 15 minutes from introduction of sample to the strip, observing through the window in the housing whether a line of color has formed, indicating the formation of a labelled antibody-antigen-immovable antibody reaction product and confirming the presence in the sample of the target carbohydrate antigen.

55 As an article of manufacture, an ICT device comprising a housing equipped with a view window in which is laterally disposed a strip of bibulous material comprising at least

1) a sample receiving zone at one end of said strip,

2) a first zone positioned in the sample flow path near the sample receiving zone, in which zone has been pre-deposited a movable deposit of prelabelled antibodies, which antibodies have been obtained from step (c) of Claim 53 and are characterized by enhanced specificity to a target carbohydrate antigen known to be characteristic of a selected species, or a selected serogroup of a species, of bacteria, and have been labelled with a labelling agent selected from among those labelling agents which display a visible color upon the formation of a labelled antibody-antigen-immovable antibody reaction product, and

3) a second zone positioned so that it is observable through the view

window of the housing of the device and is in the sample flow path close to the end of said strip that is opposite to the end where the sample receiving zone is located, in which zone a portion of unlabelled antibodies have been immovably bound to said strip, said antibodies having also been obtained from step (c) of Claim 53 and being characterized by enhanced specificity to the same target antigen known to be characteristic of the same selected species, or the same selected serogroup of a species, of bacteria as the antibodies contained in the movable conjugate deposited in said first zone.

56 The ICT device of Claim 55 wherein the antibodies in the conjugate movably deposited in said first zone and the identical antibodies immovably bound to the strip in said second zone have enhanced sensitivity to a selected target carbohydrate antigen known to be characteristic of a selected species, or a selected serogroup of a species, of Gram-negative bacteria;

57 The ICT device of Claim 55 wherein the antibodies in the conjugate movably deposited in said first zone and the identical antibodies immovably bound to the strip in said second zone have enhanced sensitivity to a selected target carbohydrate antigen known to be characteristic of a selected species, or a selected serogroup of a species, of gram-positive bacteria;

58 The ICT device of Claim 55 wherein the antibodies in the conjugate movably deposited in said first zone and the identical antibodies immovably bound to the strip in said second zone have enhanced sensitivity to a selected target carbohydrate antigen that is a

capsular polycarbohydrate antigen characteristic of a selected species, or a selected serogroup of a species, of either gram-negative or gram-positive bacteria;

59 An ICT device according to claim 55 wherein the antibodies in the conjugate movably deposited in said first zone and the identical antibodies immovably bound to the strip in said second zone are present in each zone in a concentration between 7.7 nanograms and 385 nanograms per square millimeter of surface area of said strip;

APPENDIX B--AMENDED CLAIMS

23 The method of claim 53 in which the species, or serogroup of a species, of bacteria in step (a) are gram-negative bacteria and the crude target carbohydrate antigen component thereof sought to be detected in step (d) is a lipopolycarbohydrate;

24 The method of claim 53 in which the species, or serogroup of a species, of bacteria in step (a) are gram positive bacteria and the crude target carbohydrate antigen component thereof sought to be detected in step (d) is a lipoteichoic acid, a teichoic acid, or a derivative of either;

25 The method of claim 53 in which the species, or serogroup of a species, of bacteria in step (a) are either gram-negative or gram-positive bacteria and the target carbohydrate antigen component thereof sought to be detected in step (d) is a capsular polycarbohydrate antigen;

28 The method of claim 53 wherein the liquid sample of step (d) is a natural fluid of mammalian origin;

29 The method of claim 28 wherein the liquid sample of step (d) is human urine;

30 The method of claim 28 wherein the liquid sample of step (d) is obtained from a human patient exhibiting clinical signs of a disease known to be caused by the selected species, or selected serogroup of a species, of bacteria referred to in step (a);

31 The method of claim 53 in which step (d) is an immunoassay process;

32 The method of claim 31 in which step (d) is an immunochromatographic ("ICT") process;

33 The method of claim 32 in which the bacteria referred to in step (a) are *Haemophilus influenzae* type b bacteria and the crude target carbohydrate antigen sought to be detected in step (d) is the capsular carbohydrate antigen of those bacteria;

35 The method of claim 54 in which the bacteria are gram-negative bacteria and the characteristic crude target carbohydrate antigen sought to be detected is a lipopolycarbohydrate antigen;

36 The method of claim 54 in which the bacteria are gram-positive bacteria and the characteristic crude target carbohydrate antigen sought to be detected is a lipoteichoic acid, a teichoic acid, or a derivative of either;

37 The method of claim 54 in which the bacteria are gram-positive or gram-negative bacteria and the characteristic crude target carbohydrate antigen sought to be detected is a capsular carbohydrate antigen;

38 The method claim 54 in which the liquid sample is a natural fluid of mammalian origin;

39 The method of claim 38 in which the liquid sample is human urine;

40 The method of claim 39 in which the liquid sample is obtained from a human patient exhibiting symptoms of a disease known to be caused by the species, or serogroup of a species, of bacteria of which the crude target carbohydrate antigen is known to be characteristic;

41 The method of claim 54 in which the labelling agent is finely divided gold;

42 The method of claim 39 in which the crude target carbohydrate antigen sought to be detected is the capsular carbohydrate antigen of *Haemophilus influenzae* type b;

selected

53 A method for detecting the presence in a fluid sample of a target carbohydrate antigen unique to a species, or a serogroup of a species, of bacteria which comprises the following steps:

(a) obtaining from a culture of the species, or serogroup of a species, of bacteria an embodiment of said selected target carbohydrate antigen that is essentially protein-free,

(b) coupling said essentially protein-free embodiment of said selected target carbohydrate antigen from step (a) to a chromatographic affinity gel,

(c) passing polyclonal antibodies raised in a mammal against said bacteria or said selected target carbohydrate antigen, over the chromatographic affinity gel obtained in step (b) and eluting there from antibodies with enhanced specifity to the said selected target carbohydrate antigen, and

(d) conducting an assay upon a liquid sample suspected of containing the selected target carbohydrate antigen in crude form, which assay comprises the steps of

(i) contacting the liquid sample with a detection agent comprising antibodies with enhanced specificity to said selected target carbohydrate antigen obtained in step (c) hereof, at least a portion of which have been labelled with a labelling agent known to manifest a detectable characteristic upon the formation of a reaction product between said antibodies and said selected crude target

carbohydrate antigen and

(ii) detecting the presence in the sample, when present, of said selected crude target carbohydrate antigen by observing the manifestation of said detectable characteristic therein

54 The method of Claim 53 in which step (d) comprises an ICT assay conducted in an ICT device comprising a strip of bibulous material disposed laterally within a housing, which housing is equipped with a view window and wherein said strip of bibulous material comprises at least (1) a first zone in which is deposited, at a location near the sample receiving end of the strip a movable deposit of antibodies obtained in step (c) of Claim 53 having enhanced specificity to said selected target carbohydrate antigen, which antibodies have been labelled prior to being so deposited with a labelling agent selected from among those labelling agents which display a visible color change upon the formation of a labelled antibody-antigen-immovable antibody reaction product, and (2) a second zone so positioned that it is near the opposite end of said strip relative to the first zone and is observable through the view window in the housing of said ICT device, in which another portion of antibodies obtained in step (c) of Claim 53 have been immovably bound to said strip, and the ICT assay is carried out by;

(a) contacting said liquid sample with said strip at its sample receiving end,

(b) allowing said sample to flow laterally into said first zone and pick up said movable deposit of labelled antibodies that has been placed there,

(c) allowing said sample and said labelled antibodies to flow together

laterally to said second zone while in intimate contact with one another, thereby enabling said selected target carbohydrate antigen, if present in the sample, to react at least partially with said labelled antibodies to form labelled antibody-antigen conjugates,

(d) allowing the laterally flowing stream from step (C) to flow into said second zone and contact said antibodies immovably bound to said strip and

(e) within approximately 15 minutes from introduction of sample to the strip, observing through the window in the housing whether a line of color has formed, indicating the formation of a labelled antibody-antigen-immovable antibody reaction product, which formation confirms the presence in the sample of the selected target carbohydrate antigen.

55 As an article of manufacture, an ICT device comprising a housing equipped with a view window in which is laterally disposed a strip of bibulous material comprising at least

1) a sample receiving zone at one end of said strip,

2) a first zone positioned in the sample flow path near the sample receiving zone, in which zone has been pre-deposited a movable deposit of prelabelled antibodies, which antibodies have been obtained from step (c) of Claim 53 and are characterized by enhanced specificity to a selected target carbohydrate antigen known to be unique to a species, or a serogroup of a species, of bacteria, and have been labelled with a labelling agent selected from among those labelling agents which display

a visible color upon the formation of a labelled antibody-antigen-immovable antibody reaction product, and

3) a second zone positioned so that it is observable through the view window of the housing of the device and is in the sample flow path close to the end of said strip that is opposite to the end where the sample receiving zone is located, in which zone a portion of unlabelled antibodies have been immovably bound to said strip, said antibodies having also been obtained from step (c) of Claim 53 and being characterized by enhanced specificity to the same selected target carbohydrate antigen known to be unique to the same species, or the same serogroup of a species, of bacteria as the prelabelled antibodies movably deposited in said first zone.

56 The ICT device of Claim 55 wherein the antibodies in the conjugate movably deposited in said first zone and the identical antibodies immovably bound to the strip in said second zone have enhanced sensitivity to a selected target carbohydrate antigen known to be unique to a species, or a serogroup of a species, of Gram-negative bacteria;

57 The ICT device of Claim 55 wherein the antibodies in the conjugate movably deposited in said first zone and the identical antibodies immovably bound to the strip in said second zone have enhanced sensitivity to a selected target carbohydrate antigen known to be unique to a species, or a serogroup of a species, of Gram-positive bacteria;

58 The ICT device of Claim 55 wherein the antibodies in the conjugate movably deposited in said first zone and the identical antibodies immovably bound to the strip in said

second zone have enhanced sensitivity to a selected target carbohydrate antigen that is know to capsular polycarbohydrate antigen unique to a species, or a selected serogroup of a species, of either Gram-negative or Gram-positive bacteria;

59 An ICT device according to claim 55 wherein the antibodies in the conjugate movably deposited in said first zone and the identical antibodies immovably bound to the strip in said second zone are present in each zone in a concentration between 7.7 nanograms and 385 nanograms per square millimeter of surface area of said strip;

APPENDIX C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE:	U.S.S.N. 09/518,165	
FILED:	March 1, 2000	
		GROUP ART UNIT: 1641
INVENTORS:	V.A. Koulchin , N.J. Moore, E.V. Molokova and M.K. Fent	
		EXAMINER: Ja-Na Hines
TITLE:	METHOD FOR DETECTING THE PRESENCE OF TARGET BACTERIA OR A TARGET COMPONENT CARBOHYDRATE ANTIGEN THEREOF	

DECLARATION

I, William J. Palin, being duly advised that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001, and that such willful false statements and the like may jeopardize the validity of the application or of any patent resulting therefrom, solemnly declare that all of the following statements made herein of my own knowledge are true and all of the following statements made on information and belief are believed to be true:

On that basis, I declare as follows:

1. I am presently Vice President of Research at Binax, Inc., assignee of the captioned patent application. I joined Binax, Inc. in 2001, having already spent some 35 years actively engaged in immunology research and development.

2. More specifically, after receipt in 1966 of my B.A. degree from Providence College, Providence, R.I. where I majored in Biology, I joined the 6th U.S. Army Medical Laboratory at Fort Baker, CA as a Biological Sciences Assistant and was immediately assigned to the Adenovirus Surveillance Project. During my three years there, I primarily worked on that project, but I also developed a new indirect fluorescent antibody assay for detecting Rubella antibody in patient samples.

3. In 1969, I entered the University of Minnesota at Minneapolis in the Department of Microbiology as a Research Assistant and graduate student. My research, on which I wrote a thesis entitled "Endotoxin Immunity" involved defining the structure and function correlates and the immunological specificity in the Lipid A portion of this lipopolysaccharide, and I also developed a radioimmunoassay to study antibody reactivity to Lipid A. In 1975 I received the Ph.D. degree and during 1976-1977 I did postdoctoral work, as an NIH Fellow, in the Department of Medicine at UCLA. During this period, I developed a method for monitoring endotoxemia in mammals using a sensitive gas chromatographic-mass spectrometry assay for β-hydroxymyristate.

4. Following my postdoctoral work, I have held several positions with major companies, as Senior Scientist initially, and later, as Assistant Director and as Director of Research and Development, in which I have worked on and/ or supervised the development of a variety of immunoassays for various purposes. I commenced work on assays for bacterial carbohydrate antigens while employed at Abbott Laboratories in 1977 and have continued work involving various assays of that type throughout my career. I have also worked extensively on assays for antibodies, enzymes, viruses and other substances.

5. I have read U.S. Patent Application Ser No. 09/518,165 and each of the applications Ser No. 09/139,720, 09/397,110, and 09/485,998 referred to therein. I am familiar with the Binax immunochromatographic assays for *Legionella pneumophila* serogroup 1 and *Streptococcus pneumoniae* which are sold under the trademark NOW and are respectively described in U.S. Patent Applications Serial Nos. 09/139,720 and 09/397,110. I am also familiar with the records of work done on these assays, each of which depends on detecting a characteristic carbohydrate antigen of the bacterium in a fluid from a human patient.

6. I have also carefully read the Office Action dated March 20, 2003 and I have been asked to comment upon the validity and practicality of various evidentiarily unsubstantiated assumptions appearing therein. I have also been supplied with and carefully read the seven-page document "Critical Synergy: The Biotechnology Industry and Intellectual Property Protection, Presentation at the

October 17, 1994 Hearing of the U.S. Patent and Trademark Office, San Diego, CA" allegedly published by the Biotechnology Industry Organization, Washington, D.C., pages 100-107 cited at page 6 of the Action. I could find nothing in this document about immunoassays, antigens, antibodies, bacteria or immunology and see nothing in the Office Action that justifies any attempted analogy between this application Serial No. 09/518,165 and the subject matter that the document *does* discuss.

7. The Office Action ignores that there was a vast body of literature available as of March 1, 2000 when Application Ser. No. 09/518,165 was filed that pertains to the various *facts* concerning immunology that underlie this application. The existence of this body of literature, which comprises published articles, dissertations, lectures and other writings from persons located worldwide that are easily locatable through searches of widely available data bases (such as the National Library of Medicine's Pub Med and Biosis ~~515~~ ™ , but by no means limited thereto), patents from various countries, literature from suppliers of equipment and reagents which is frequently highly informative about the capabilities and capacities of equipment, the compatibility and conditions of use of reagents, etc. For example, Polysciences, Inc. puts out a catalog that devotes some eight pages to the variations in linkage technology that may be availed of to link a ligand to an affinity chromatography column and another eight pages to the various affinity matrices it has available. For another example, Sigma Chemical Co. lists 30 different affinity matrices in its catalog and makes

available to customers, including their researchers, technical services employees highly knowledgeable about these matrices who will consult with customers by telephone, e-mail or fax about the properties of the matrices, and if needed, will recommend the one best adapted to a specific task, as well as provide assistance in solving or avoiding various problems associated with particular matrices.

8. In particular, this vast body of literature includes writings describing previous work in which carbohydrate antigens indigenous to the bacteria that are known to cause infectious diseases were identified and methods for separating them from bacterial cultures were described. The literature also includes many articles relating to methodology for minimizing the protein content of carbohydrate antigens. The literature likewise describes many uses of affinity chromatography for antibody purification.

9. At Binax, bacteria for culturing and for antibody induction in host animals is almost always obtained from Centers for Disease Control or from one of the established depositories of biological materials, such as American Type Culture Collection or Pasteur Institute. These bacteria are provided to Binax with information specifying their species and serotype and giving recommendations for their culture which include recommendations as to culture medium and other growing conditions. Laboratories such as that at Binax and the laboratories of other companies where I have previously been employed (which include Abbott, Becton Dickinson and Idexx Corporation) conduct research that is targeted toward developing useful and operable products for sale. Such laboratories are

geared toward accepting and following the well-documented observations of product and equipment suppliers about details of how to use and otherwise treat the supplied materials, while focusing upon the aspects of their research and development that are important to developing a useful diagnostic test.

10. The invention described in Application Ser. No. 09/518,165 involves the discovery that crude antibodies to bacterial carbohydrate antigens acquire greatly enhanced specificity and sensitivity toward the corresponding antigen, whether that antigen is present as a part of a whole or partial bacterium or is in free form in a human bodily fluid, if the crude antibodies have been affinity purified by passing them over a chromatographic affinity column to which has been coupled an embodiment of the target antigen that is essentially protein-free (i.e contains not more than 10% protein and preferably less).

11. In my opinion, this invention can readily be practiced by a person of ordinary skill in the art by simply following the teachings of the application and combining those teachings with prior art teachings, especially those available as of the application filing date, March 1, 2000, which relate to the particular bacterium and its characteristic carbohydrate antigens. In other words, application 09/518,165 in its examples describes exactly how the invention is applied to (1) obtain an essentially protein-free carbohydrate antigen of *Haemophilus influenzae* type b, (2) couple that essentially protein-free carbohydrate antigen to a chromatographic affinity column, (3) pass crude antibodies to *H. influenzae* type b over the column and (4) use the thus treated

antibodies in an ICT assay for the crude carbohydrate antigen of which the essentially protein-free carbohydrate antigen employed in step (2)is an embodiment. The incorporated by reference examples of Serial No. 09/139,720 describe how an essentially protein-free carbohydrate antigen of *Legionella pneumophila* serogroup 1 was obtained from a culture of those bacteria, how the essentially protein free carbohydrate antigen was coupled to a chromatographic affinity column, how crude antibodies to the bacteria were passed over the column and rendered antigen-specific and how the treated antibodies were then utilized in an ICT assay which is currently and has since September 1998 been sold for use as a diagnostic tool by Binax, Inc., under the trademark NOW®, to detect the crude carbohydrate antigen in human bodily fluid samples. The incorporated by reference examples of Serial Nos. 09/156,486 and 09/397,110 describe how an essentially protein-free embodiment of the cell wall carbohydrate antigen indigenous to all serotypes of *S. pneumoniae* was obtained from a bacterial culture and coupled to a chromatographic affinity column, how crude antibodies to the bacteria were passed over the column and rendered antigen-specific and how the treated antibodies were then employed in an ICT assay which is currently and has since August 1999 been sold for use as a diagnostic tool by Binax, Inc., also under the NOW ® trademark.

12. Each of the three assays referred to in ¶11 hereof commenced with the recognition of the need for a highly sensitive, fast and easily usable assay that would permit rapid diagnosis of a specific disease state and with an examination of what the prior literature showed with respect to efforts to produce these tests and the target antigens employed in them. In each case tentative selection of a target carbohydrate antigen was made based on known characteristics of the disease and/or the antigen. This is described on page 11, middle paragraph, of application Serial No. 09/518,165. A similar practical selection, using assistance from the literature, was followed at Binax in selecting target carbohydrate antigens for diagnostic assays relating to other bacteria-caused diseases now being developed there. The application at page 11, middle paragraph, and page 12, first full paragraph, would lead any person of ordinary skill in immunology who wished to devise an assay enabling diagnosis of a particular bacteria-caused disease state to consult the existing literature as an aid to selecting a bacterial carbohydrate target antigen for the assay.

13. Application 09/518,165 also clearly teaches that, for separating the selected target carbohydrate antigen from a bacterial culture, one should consult the literature. See p.14, lines 3-5 of the specification and also p.25, last paragraph. These teachings about referring to the literature show that what is already known clearly also applies to rendering the carbohydrate antigen "essentially protein-free" as that term is defined in the application. It is noted that it is also well within the ordinary skill of the art in immunology to adapt product

separation and protein minimization techniques that have been published for a related carbohydrate antigen to a selected target antigen having similar functionality or composition.

14. The specification of Serial No. 09/518,165, including the information incorporated by reference, contains specific teachings about the coupling of the "essentially protein-free" carbohydrate antigen to a suitable affinity matrix, and the passage of raw antibodies thereover. A person of ordinary skill in immunology with such additional help from the literature and/or a supplier of affinity matrices as might be desired, would have no difficulty in performing this step efficaciously.

15. The specification of Serial No. 09/518,165 including the information incorporated by reference, describes in detail the preparation of an immunochromatographic strip with a "capture line" of immovable affinity purified antibodies striped across the strip near the end most remote from sample introduction and a movable deposit of gold-labelled affinity-purified antibodies placed near the point of sample introduction. The specification teaches that other labels may be used in lieu of gold. It also cites references that teach modes of conjugating gold to antibodies and other ligands. A great deal of technical literature about labels and methods for conjugating them to ligands exists. The teachings in the application, including those incorporated by reference about the preparation of the ICT strips for detecting target carbohydrate antigens of *Legionella pneumophila* serogroup 1 and *Streptococcus*

pneumoniae, are informative and, in my opinion, could readily be followed by a person of ordinary skill in immunology, working with antibodies raised to either the host bacteria of the antigen or an Ig G cut of the selected carbohydrate antigen thereof and then affinity-purified as described in application 09/518,165, to arrive at a useful and potentially highly successful diagnostic test.

16. With specific reference to the office action:

(a) Page 6, 2nd paragraph, states. "For example, the specification at page 14 teaches different purification of carbohydrate antigen steps, including an incubation step, sonication steps, repeated precipitation and centrifugation steps, lyophilization, subjected to Lowry assay and for proteins and tested for carbohydrates by phenol-sulfuric acid method."

First of all, this listing is taken from the specific exemplification relating to *Haemophilus influenzae* type b. Secondly the only "step" listed that pertains to purification of antigen *per se* is the "repeated precipitation and centrifugation" step. Thirdly, there is no "sonication" step referred to on page 14 of the specification of Application Serial No. 09/518,165. Perhaps most importantly, I understand the disclosure of this application to teach that any known method of obtaining the desired antigen from a culture of the bacteria may be used, so long as care is taken to ensure that the antigen is recovered in essentially protein-free form as defined therein--i.e., containing not more, and preferably less, than 10% of protein by weight.

(b) The action then states:

> "It is well known in the art that specific bacterial species require specific extraction methods, yet the claims do not take this into consideration and generically claim a method of detection".

I understand that the Examiner is here speaking of "extraction" of the antigen from bacteria *contained in a sample* that is to be assayed according to the general ICT method recited in certain of the claims. The premise that antigen must be extracted from bacteria contained in a sample of human bodily fluid, however, is inconsistent with the experiences of Binax in that Binax has found it to be unnecessary to take steps to "extract" the carbohydrate antigen from bacteria in such samples in order to run and complete a satisfactory assay.

Further, the many entities that have purchased and satisfactorily used the Binax NOW® tests for *Legionella pneumophila* serogroup 1 and *Streptococcus pneumoniae* have successfully performed well over a million assays on human bodily fluids without manifesting any need to "extract" antigen from bacteria contained in human fluids.

(c) I have been advised by counsel that the Examiner's position relating to "extraction" probably relies upon the teaching of Imrich *et al* U.S. patent 5,415,994 wherein "an extraction chamber" is provided and the sample on a swab is delivered to this zone and treated with an "extraction solution" prior to the assay of the sample. See col.2, lines 26-40; see also col.1, l.67 to col.2, l.9 wherein prior art is identified that apparently alludes to the alleged need for "extraction" in order for optimal detection of the bacterium by monoclonal antibodies. It is not clear whether the Imrich *et al* group actually ever worked with liquid samples, even though these are mentioned at col.3, lines 11-13 as being operable in the method disclosed. "Pharyngeal exudates", to which reference is made at col.1, l.55; col.3, lines 12-

13 and col.4, line 16 appear to be of special concern in this patent. A "pharyngeal exudate" is often a mass of highly viscous semi-solid material that has lodged in the nose or throat and has not passed through human organs that are now known to destroy the cell walls of bacteria, such as the kidney and /or the liver, or been subjected to the action of stomach acids or digestive enzymes, both of which also "open up" bacteria. Pharyngeal exudates are also often characterized by substantial presence of live bacteria which are growing and reproducing and are sometimes harder to "open" than the partial fragments of bacteria prevalent in blood, urine, spinal fluid and other bodily liquids. It is further noteworthy that Example 2, the only specific example of an actual assay, was conducted on killed *whole* Group A *Streptococcus* bacteria, which at least impliedly had intact cell walls. In short, the Imrich *et al* patent, as I understand it, says nothing inconsistent with the Binax experience that *no* "extraction" of bacteria contained in human or other mammalian *liquid* samples, (which are the samples of choice to be used in the assays covered by the present application) is necessary.

I also note that *Streptococcus pyogenes* (commonly called Strep A) is well known to immunologists as requiring a more rigorous and harsh "extraction" treatment than most bacteria. This treatment is normally made with ~~mono~~micro nitrous acid at pH2, in order to expose its target carbohydrate antigen to recognition by antibodies. Accordingly, this bacterium cannot be relied on for purposes of generalization in respect of need for "extraction" of samples suspected of containing target antigens. By contrast, such bacteria as, e.g. *Streptococcus pneumoniae* and various *Haemophilus* species are well-known to undergo spontaneous lysis or splitting of cell walls. This spontaneous lysis is also known as autolysis.

Still further, I note that in instances where extraction may be needed because of the occurrence in samples of bacteria having intact cell walls, the science of immunology, as applied to disease causing bacteria, is so well-developed that the literature contains a substantial body of information about how particular bacteria species should be "extracted" when this is found to be needed. This literature is well known and readily available to immunologists generally. An immunologist wishing to follow the process of Application Serial No. 518,165 and develop an ICT test for detecting a carbohydrate antigen of a bacterium likely to possess intact cell walls when present in a bodily fluid would normally be aware of this problem at the commencement of the development work and would have determined from the literature the nature of the cell wall splitting reagents likely to be needed in an actual test protocol.

(d) I state unequivocally that the disclosure at page 20 in Section C "Immunoassay Procedures" of Application Serial No.09/518,165 of the addition of three drops of "Reagent A" consisting of Tween 20, sodium azide and sodium dodecyl sulfate in sodium citrate phosphate buffer to the sample does not have the purpose to "produce the crude carbohydrate antigen" as alleged in at page 8 of the Office Action and does not produce that result. In the Binax NOW ® ICT tests and in Application Serial No. 09/518,165, "Reagent A" has a dual function. Typically, the volume of liquid sample is not sufficient to ensure that the sample will flow through the immunochromatographic medium. The addition of Reagent A augments the sample volume sufficiently to ensure that flow occurs with enough momentum to pick up and carry with it the labelled antibodies that have been movably deposited in the flow path. Secondly, the components of this Reagent A are a buffer, salts and surfactant. The

buffer and salts provide a milieu that facilitates the reaction of antigens in the sample with labelled antibodies that occurs during flow and the further reaction of labelled antibody-antigen reaction products with immobilized antibodies that occurs at the capture line. The surfactant present has the function of reducing the non-specific binding that often occurs during tests.

(e) The Office Action's reference to the different "Reagent A"--i.e., tris base containing the zwitterionic detergent SB3-8--is unrelated to any requirement of Application Serial No. 09/518,165. First of all, "Reagent A" is a generic term that Binax applies to *any* additive it places in a commercial assay kit. The term "Reagent A" is not directed to the composition or purpose of the additive. It is simply a convenient term. The particular purpose of the Reagent A additive selected for a particular test is always addressed in the leaflet included in the specific kit for that test. Secondly, Application Serial No. 09/458,998 involves use of the same affinity-purified antibodies described in Serial No. 09/139,720–but in an enzyme immunoassay for *Legionella* bacteria, especially *Legionella pneumophila* serogroup 1, in environmental water. Application Serial No. 09/458,998 hence is *not* directed to the same process invention and ICT test protocol that appears in each of applications Serial Nos. 09/139,720, 09/156,486, 09/397,110 and 09/518,165. Rather, Serial No. 09/458,998 involves a different use for the affinity-purified antibodies of *Legionella* bacteria from that of detecting in a fluid from an infected human patient a carbohydrate antigen that enables identification of the bacterium to which that antigen is indigenous as the agent causative of the patients disease state. In application Serial No. 09/458,998, bacteria to be assayed have been growing in water in old pipes and other structures of heating/air-conditioning systems, in pools of stagnant water, and in other still water. These bacteria have intact cell walls and in some cases are also

contained within strong husklike structures. To assay for the crude carbohydrate antigen of such bacteria, the bacteria do often need to be opened up, either mechanically or by an extraction agent or both. Such opening of cell walls is the function of the tris base/SB3-8 reagent in application 09/458,998.

(f) The function of this latter tris base/SB3-8 reagent relative to enabling an assay for the presence of *Legionella* bacteria present in environmental water is *not* related to how one may "achieve purification of an essentially protein-free carbohydrate antigen" as implied in the last sentence on page 8 of the office action. Rather, the tris base/SB3-8 reagent is used to open up or aid in opening up the cell wall and/or the husklike structure of *Legionella* bacteria present in environmental water so that the target carbohydrate antigen is available to be detected by the reagents used to perform the enzyme immunoassay described in Application Ser. No. 09/458,998. No such opening up is needed to perform the described ICT assays of Applications Ser. Nos. 09/139,720; 09/156, 486; 09/397,110 or 09/518,165, in each of which the substance to be assayed is a human bodily fluid.

(g) The Office Action at page 9 states "the instant claims fail to distinguish between detecting gram negative and gram positive bacteria by separate method steps". The suggestion, apparently, is that the methodology for detecting gram positive and gram negative bacteria in an ICT immunoassay should somehow involve different method steps. But application 07/139,720 shows how, by selecting a carbohydrate antigen known to be characteristic of *Legionella pneumophila* serogroup 1, obtaining it in essentially protein-free form, applying it to an affinity column, purifying crude antibodies raised either to the bacteria or to tan Ig G cut of the same antigen by passing the antibodies over the purified antigen on the

column and using the thus purified antibodies in the described ICT test to detect the crude antigen in a test sample of human bodily fluid, the presence of the bacterium is necessarily detected. *Legionella pneumophila* serogroup 1 is a Gram stain negative bacterium as the office action appears to concede at page 15. Application Ser. No. 09/397,110 and its parent application teach employing *the same* steps commencing by obtaining the essentially protein-free carbohydrate antigen--this one known to inhere in all serotypes of *Streptococcus pneumoniae*--followed by applying the essentially protein-free antigen to a chromatographic affinity column, passing antibodies raised to either *S. pneumoniae* or an Ig G cut of the crude carbohydrate antigen over the column to purify them and using the antibodies in the same ICT test configuration to detect the same carbohydrate antigen in crude form in a test sample of human bodily fluid. As page 15 of the office action indicates, *Streptococcus pneumoniae* is a Gram stain positive bacterium. The process covered by application Ser. No. 09/518,165 obviously applies to both gram negative and gram-positive bacteria and as such, it is not intended to and does not "distinguish between detecting gram negative and gram positive bacteria by separate method steps" as Office Action (p.9) implies it should. The process instead is one that is generic to bacteria. By selecting a target antigen specific to a particular species or serogroup of a species of bacteria, obtaining the antigen in a form containing not more and preferably less than 10% protein, using this form of antigen to affinity-purify antibodies raised either to the bacteria or an Ig G cut of the crude antigen, incorporating the affinity purified antibodies in the ICT test strip format as described in Application Ser. No. 09/518,165 and then using the ICT test strip to assay a bodily fluid sample from a person suspected of harboring a disease caused by the bacteria, one can identify the same antigen in its

crude form, if present in the sample, with very high specificity and can accordingly diagnose and prescribe for the disease speedily. On the other hand, if the assay is negative for the target antigen, disease caused by the bacteria species (or serogroup of a species) to which the target antigen is specific can speedily be ruled out.

(h) The Office Action, p.9, states

> "The broad and generic claims encompass detecting at least species or serogroup of any bacteria, thereby including detecting multiple species in the manner claimed. If applicant does not intend for the claims to encompass such the applicant should narrowly tailor the claims to only encompass what is taught and supported by the instant specification".

This office action statement is very confusing and contradictory. The claims are intended to cover detecting bacteria species where the target carbohydrate antigen selected is characteristic of an entire species, *or* a serogroup of a species, in instances where the target carbohydrate antigen selected is characteristic *only* of a serogroup of a species. What the application teaches is a generic method for detecting a carbohydrate antigen that is characteristic of either a species of bacteria, *or else* a serogroup of a species of bacteria. The method, as already stated, involves (1) obtaining from a culture of the bacteria the target antigen of the detection in a form containing no more than 10%, and preferably less than 10%, of protein, (2) conjugating that antigen containing no more than 10% protein to a chromatographic affinity column, (3) affinity purifying antibodies (raised against either the bacteria or against an Ig G cut of the crude antigen) by passing said antibodies over the affinity column to which the antigen containing no more than 10% protein is conjugated; (4) conjugating one portion of the antibodies thus purified to a label and depositing the label-antibody conjugate movably on an ICT strip near the site of sample introduction; (5) immovably striping another portion of the

antibodies thus purified across the ICT strip near the end opposite to the site of sample introduction and (6) performing an assay by introducing a sample of human bodily fluid to the strip and allowing the sample to flow laterally along the strip so that it picks up the movably deposited label- antibody conjugate and flows therewith to the immovably striped line of unlabelled antibodies and (7) observing whether a color forms along the immovable stripe, denoting the formation of a "sandwich" of labelled antibody-antigen from sample-fixed antibody and therefore the presence of target antigen in the sample.

If the quotation from the Office Action intends to suggest that the ICT strip *could* have multiple movable deposits of *different* labelled affinity purified antibodies and multiple immovable stripes of affinity-purified antibodies so selected that each movable deposit contains purified antibodies different from each other, but identical to the antibodies in one of the immovable stripes so that a single sample of human bodily fluid could be simultaneously assayed for the presence or absence of multiple carbohydrate antigens, each such antigen being characteristic of a different bacteria species or a different serogroup of another species, this is entirely possible and even desirable within the scope of this invention. Such an assay may have the attribute of permitting a physician to use one ICT test on one sample to rule out certain bacteria as causative of a patient's disease state while also locating the one species, or serogroup of a species, of bacteria that *is* causative. In such a test for target carbohydrate antigens of multiple bacteria species, target carbohydrate antigens of multiple serogroups of bacterial species, or some combination of target carbohydrate antigens of some bacteria species and target carbohydrate antigens of serogroups of some bacteria species, it is of no importance which bacteria are gram-negative and which bacteria are gram-positive. What is important is

that each target carbohydrate antigen be characteristic of only the bacteria species, or only the serogroup of a species, in which it is found, so that whether the tests be run separately or simultaneously on the same strip, a negative test will mean that the bacteria species, or serogroup of a bacteria species, of which the target antigen is characteristic is not present in the patient sample and is not responsible for the patient's disease state, while a positive test will indicate that the bacteria species, or serogroup of a bacteria species, of which the target antigen is characteristic *is* present in the sample and (provided this presence is consistent with the patient's clinical symptoms), is highly likely to be causative of the disease state. If the quoted statement is intended to suggest that some particular carbohydrate antigen exists which is characteristic of both one or more gram-positive and one or more gram-negative bacteria, however, that is contrary to present knowledge in the art and not encompassed by application Serial No. 09/518,165.

(i) The office action at p. 9 further states:

> "Applicants statements that specific sample types perform extraction on some bacteria only bolsters the examiner's position that broad generic techniques cannot apply to all types of bacteria in any type of sample."

This statement is very hard to understand. I am informed and I believe that "Applicants" have not stated that *any* "sample types" perform extraction on bacteria. Furthermore, types of samples to be assayed do *not* and cannot "perform extraction" on the bacteria or bacteria fragments they may contain. I am further informed that Applicants *have* stated that the only instance in any presently-pending or issued Binax patent application where "extraction"of bacteria is important to enable the successful and accurate performance of an assay is the one

described in pending Application Ser. No. 09/458,998 wherein the living *Legionella* bacteria growing in environmental water, which have strong intact cell walls and in some cases, husk-like covers as well, must often be mechanically macerated and/or treated with tris base containing SB3-8, a zwitterionic detergent, in order to open their carbohydrate antigens up to the action of affinity-purified antibodies. In environmental water, however, the ICT test which is the last step of the generic process of the present invention and which was designed and intended to be run on samples of human (or mammalian) bodily fluids is not a satisfactorily informative test for identifying the presence of live *Legionella* bacteria--as application Serial No. 09/458,998 in fact teaches. In the application Serial No. 09/518,165 where the samples contemplated are in all instances human bodily fluids such as urine, blood, saliva, spinal fluid, and the like, extraction has not been found to be needed. See ¶10(c) above.

(j) The paragraph of the action bridging pages 9 and 10 of the action is not readily comprehensible to me. The specification of application 09/518,165 at p.2 under the heading "BACKGROUND OF THE INVENTION" states that

> "Gram-negative bacteria are known to have in common the possession of at least one lipo-polysaccharide or other lipo-carbohydrate antigen, while Gram-positive bacteria are known to possess the common characteristic of having at least one carbohydrate antigen that is a lipo-teichoic acid or a teichoic acid or a derivative of either."

This is a recitation of information that is well-known in the art of immunology and has been so known throughout my own career in the field.

The application says nothing about making derivatives from the crude target antigen, nor do I perceive any reason why it should do so. Applicants here are not in engaged in making derivatives of the target antigens or in substituting such derivatives for the carbohydrate antigens that are indigenous to a particular bacteria species or serogroup of a species. The invention contemplates *only* that an embodiment of the selected target carbohydrate antigen be rendered "essentially protein-free"--i.e. that its protein content be reduced to not more than 10% by weight and preferably less--and that that essentially protein-free antigen embodiment be applied to a chromatographic affinity column and used to purify antibodies which are then used to detect the crude embodiment of the same antigen in a sample of human bodily fluid. There is no occasion for "one of skill in the art...to perform experimentation to use derivatives of either lipoteichoic acid or teichoic acid to detect the crude antigen" as postulated at p.10 of the Office Action. *If* a target antigen of some bacteria species, or serogroup, should happen to be a *derivative* of either teichoic or lipoteichoic acid, there is no immunological reaction in which it could be used to detect itself. Furthermore, if a target carbohydrate antigen of some bacteria species, or serogroup of a species should be a derivative of teichoic acid or lipoteichoic acid, my experience and training in immunology tell me that the antibodies, whether raised against the bacteria or against an Ig G cut of the crude antigen, will be naturally adapted to be a binding partner of that derivative, so as to insure that the natural binding affinity between antigen and antibody will be preserved and that no one will need to "experiment" about how to use them to detect the crude antigen.

(k). The conclusion on page 12, "Accordingly, one of skill in the art would be required to perform undue experimentation to use esters of either lipoteichoic acid or teichoic acid to detect the crude antigen"

is a *non sequitur*. The application Ser. No. 09/518,165 does not disclose or contemplate that esters of lipoteichoic acid or teichoic acid could or would be utilized to "detect" *any* crude antigen. The mention of teichoic and lipoteichoic acids and their derivatives at pages 2 and 9 of this application clearly relate to all of them as *carbohydrate antigens*. Carbohydrate antigens are not usable, as anyone with minimal training in immunology knows, to "detect" other antigens.

Signed this 19 day of August 2003.

William J. Paliga

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

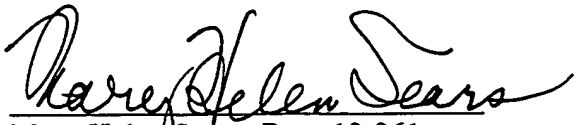
IN RE:	U.S.S.N. 09/518,165	)
FILED:	March 1, 2000	)
TITLE:	METHOD FOR DETECTING PRESENCE OF TARGET BACTERIA OR A TARGET COMPONENT CARBOHYDRATE ANTIGEN THEREOF	)
		) GROUP ART UNIT: 1645
INVENTORS:	V.A. Koulchin, N.J. Moore, E.V. Molokova and M.K. Fent	) EXAMINER: Ja-Na Hines

REQUEST FOR THREE-MONTH EXTENSION OF TIME TO RESPOND TO OFFICE ACTION MAILED MARCH 20, 2003

Request in hereby respectfully made that the time for response to the final rejection herein mailed March 20, 2003 be extended three months to expire Monday, September 22, 2003.

A check to cover the small entity time extension fee for 3 months of $465.00 accompanies this request.

Respectfully submitted,



Mary Helen Sears, Reg. 19,961
Attorney for Applicants
The M.H. Sears Law Firm, Chartered
910 Seventeenth Street, N.W., Suite 800
Washington, D.C., 20006
Telephone: (202) 463-3892
Telecopy: (202) 463-4852

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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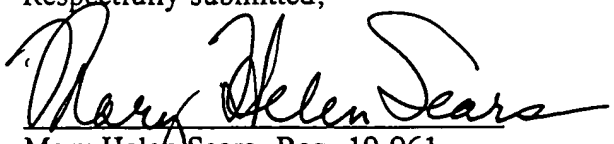
REQUEST PURSUANT TO 37 C.F.R. §1.129 FOR ENTRY AND CONSIDERATION OF FIRST SUBMISSION AFTER FINAL REJECTION

Applicants hereby respectfully request that the response to the final rejection mailed March 20, 2003 which is concurrently being filed be entered in the captioned application and considered pursuant to the provisions of 37 C.F.R. §1.129. A check for $375.00 to pay the small entity fee for filing this submission, as required in 37 C.F.R. §1.17(r) accompanies this request.

Respectfully submitted,



Mary Helen Sears, Reg. 19,961
Attorney for Applicants
The M.H. Sears Law Firm, Chartered
910 Seventeenth Street, N.W., Suite 800
Washington, D.C., 20006
Telephone: (202) 463-3892
Telecopy: (202) 463-4852